



PATENT
Attorney Docket No. EURA-004/00US
(Formerly 451194-101)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gopi M. Venkatesh et al.

Application No.: 10/713,929

Confirmation No.: 4820

Filed: November 14, 2003

Group Art Unit: 1615

**For: MODIFIED RELEASE DOSAGE FORMS OF
SKELETAL MUSCLE RELAXANTS**

Examiner: BARHAM, Bethany P.

DECLARATION UNDER 37 C.F.R. § 1.131

We, Dr. Gopi Venkatesh and James M. Clevenger declare as follows:

1. We are the named inventors of the above-noted application (Ser. No. 10/713,929)
2. We have read and understood the Official Action of January 11, 2008, and in particular the rejection of the pending claims under 35 U.S.C. §103 over the combination of U.S. Publ. No. 2004/0197407 (the '407 application) and U.S. Publ. Nos. 2003/0215496 or 2003/0099711.
3. We understand that the earliest asserted priority date of the '407 application is February 11, 2003, through the priority claim to U.S. Provisional Application Ser. No. 60/446,425.
4. The subject matter of the pending claims of the present application was invented by Gopi Venkatesh and James M. Clevenger (the named inventors) prior to February 11, 2003.
5. Example 3 of the instant application describes the formulation and production of a multiparticulate dosage form of cyclobenzaprine, wherein the cyclobenzaprine is coated on sugar spheres and covered with a water insoluble polymer to produced extended release beads (see paragraph 0045). Figure 4 of the instant application shows the release rate of the finished beads of Example 3 (e.g., **Batch 805-AAA-105**).

6. Exhibit A, dated before February 11, 2003, shows a "Master Formula" sheet documenting the production of the intermediate cyclobenzaprine coated beads used to make **Batch 805-AAA-105**. This intermediate batch (designated **Lot No. 837-AG-034**) comprises:

- "Sugar Spheres" (5475 g) coated with "cyclobenzaprine HCl" (1875 g) from "Acetone, NF 50/50% Ratio" and "USP Purified Water, 50/50% Ratio";
- seal coated with "2.00%" of "Opadry Clear YS-1-7006".

Exhibit B, dated before February 11, 2003, shows a "Master Formula" sheet documenting the actual production of **Batch 805-AAA-105** by coating the intermediate cyclobenzaprine beads of **Lot No. 837-AG-034** with an extended release water insoluble polymer:

- ER coating of **Lot No. 837-AG-034** with "Ethylcellulose 10P Premium (10 cps)" (363.6 g) and "Diethyl Phthalate" (36.4 g) dissolved in "Acetone, NF (98 parts)" and "USP Purified Water (2 parts)". Samples were collected with a coating weight of "10%" (designated **Batch or Lot No. 805-AAA-105**).

Exhibit C, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for "Lot # 805-AAA-105-10" (i.e., 10 wt.% ER coating, Batch 805-AAA-105). The data are identical to that presented in graphical form for the sample designated "10% ER Coating Wt., Batch 805AAA105" in Figure 4 of the instant application and shows that the 10% ER coated beads exhibit a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

7. Exhibit D, dated before February 11, 2003, is a batch record showing the ingredients of "Cyclobenzaprine HCl ER Beads", **Lot No. PE271EA001**:

- "Cyclobenzaprine HCl Intermediate Beads", Item code **PE249**; coated with "Ethylcellulose" and "Diethyl Phthalate".

Exhibit E, dated before February 11, 2003, documents the manufacture of "Cyclobenzaprine HCl MR Capsules, 30 mg", Lot No. **PF306EA001**:

- "White, Opaque Hard Gelatin Capsules, Size 4", filled with "Cyclobenzaprine HCl Extended Release Beads", Item code **PE271**.

Exhibit F, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for clinical batch "Lot # PF306EA001". The data are identical to that presented in graphical form for the clinical sample designated "PF306EA001" in Figure 6, Examples 4 and 5 of the instant application. Formulation PF306EA001 shows a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

8. Thus, Exhibits A and B document the production of the identical multi-particulate cyclobenzaprine dosage forms described in Example 3 of the present application, and as set forth in the instant claims, before February 11, 2003.

9. Thus, Exhibits D and E document the production of the identical clinical batch described in Examples 4 and 5 of the present application, and as set forth in the instant claims, before February 11, 2003.

10. We further declare that all statements made herein on our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Respectfully submitted,

Gopi Venkatesh

Gopi Venkatesh

2/13/2008

Date

James M. Clevenger

James M. Clevenger

2/13/2008

Date

Master Formula

Exhibit A

Product Name: Cyclobenzaprine HCl, Drug Layered Beads		Batch Number: 8374A60934		Page _____ of _____		Date: _____	
Physical Description: Off White		Capsule Size: N/A		Batch Size: 7500.0 gms			
Imprint (Uppers): N/A		Imprint (Lowers): N/A		Label (eg \ Uppr N/A		Unit Weight (eg) N/A	
Written By: A. Gallo <i>A. Gallo</i>		Reviewed By:		Room #: A72		Temperature: 64.0 °C	
ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity %	Wt/Unit	Quantity Gms/batch	Weighted By	Charged By
1	*Cyclobenzaprine HCl	C14667401	25.00	7.50	1875.0 gms	1875.0	1875
2	Sugar Spheres 20-25 Mesh (Hansen)	RD - 991114	73.00	21.90	5475.0 gms	5475.0	5475
3	*Opadry Clear YS - 1 - 7006	H10507376	2.00	0.60	150.0 gms	150.0	150
4							
5							
6							
7							
8							
9							
10	Acetone, NF 50/50 % Ratio	A10707332			2812.50 ml	2812.50	2812
11	USP Purified Water, 50/50 % Ratio	W-10002061B			2812.50 ml	2812.50	2812
12	USP Purified Water @ 10.0 % of Seal Coat	W-10002061B			1350.0 ml	1350.0	1350
Total:			100.00	30.00	7500.0 gms	7500.0	7500

Objective: to evaluate dose @ 25.0 % Using GPCG 5

• Items 10,11,12 is use to make coating solution. Both mg and g batch totals do not reflect counts.

Note: Acetone, NF / USP Purified Water 50/50 Ratio.

Exhibit B

Project No. _____
Book No. 805

TITLE CYCLOBENZAPRINE HCl EC BEADS

From Page No. 103

Purpose: To EC coat Cyclobenzaprine HCl drug layered beads using Solvent (50:50) Acetone : H₂O as a medium. The drug layered beads were then Ethyl Cellulose coated using Acetone : H₂O (98:2). The EC was done using Glatt GPCG-5 Wurster.

Master Formula

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Product Name: Cyclobenzaprine HCl - Extended Release Beads (25.0 mg)						
Physical Description: Extended Release Coating						
Lot # 805-AAA-105						
Data:						
Item #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity w/w	Quantity Mg/Unit	Quantity Cast batch	Quantity Weighed
1.	Cyclobenzaprine HCl, Drug Layered Beads	837-A0-034	3600.0		3600.0	AAA
2.	Ethylcellulose 10P Premium (10cps), NF	B11407226	363.6		364.0	AAA
3.	Diethyl Phthalate, USP	D11807500	36.4		36.4	AAA
10.	Acetone, NF (98 parts)	A10707332	5639.0		5639.0	AAA
11.	Purified Water, USP (2 parts)	W100-01	115.0		115.0	AAA
Total:						
Objective: Evaluating Dose @ 10.0 % Samples were taken @ 7, 8, 9, & 10% of EC applied.						

AAA

To Page No

Witnessed & Understood by me,

Date

Invented by

Date

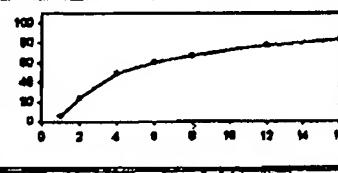
Exhibit C

Project No.
Book No. 891

113

TITLE Cystobengapic the Miss

Sample		Time		Avg. Relvd (%)		RSD		Graph	
500-A-105-10	NA	1.0	8	9.1					
		2.0	24	4.2					
		4.0	48	2.9					
		6.0	60	2.3					
		8.0	67	2.8					
		12.0	77	1.5					
		16.0	65	1.2					



To Page No. 1

Witnessed & Unsigned by me.

Don Henley

Date _____

Invented by

Date

Recorded by Yokeshon

ISSUED BY Q.A.

Eurand America, Inc.
 Cyclobenzaprine HCl ER Beads
 Batch Size: 85 kg (Theoretical)
 MF #: A-50PE271-A

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Lot #: PE271EA001	Date of Manufacturing: [REDACTED]
Effective Date: [REDACTED]	
Prepared By: [Signature]	Date: [REDACTED]
Mfg. Approval By: [Signature]	Date: [REDACTED]
R&D Approval By: [Signature]	Date: [REDACTED]
QA Approval By: [Signature]	Date: [REDACTED]
QA Issue: [Signature]	Date: [REDACTED]
QA Audited By: [Signature]	Date: [REDACTED]

Item No.	Item Code	Bead Dosage (mg/g)	% per Batch (w/w)	Ingredient Name	Theoretical Quantity Per Batch**
1	PE249	910.00	91.00	Cyclobenzaprine HCl Intermediate Beads	77.4 Kg
2	E114	81.25	8.13	Ethylcellulose, Premium Std 10cps	6.9 Kg
3	D118	8.75	0.88	Diethyl Phthalate, NF	0.75 Kg
4	A107	—	—	Acetone, NF*	116.7 Kg
5	W100	—	—	Purified Water, USP*	2.4 Kg
		1000.00	100.01	TOTAL=	85.0 Kg

*Removed from process during the drying process

**Actual batch is based on the actual quantity of the Intermediate Beads available for use. See page 2

Exhibit D

ISSUED BY Q.A.

Eurand America, Inc.

Cyclobenzaprine HCl MR Capsules, 30 mg

Batch Size - 130,000 Capsules (Theoretical))

MF#: A-60PF306-A

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Lot # PF306EA 001		Date of Manufacturing: Inci... Manufacture			
Effective Date: [REDACTED]					
Prepared By:	Date: [REDACTED]				
MFG. Approval By:	Date: [REDACTED]				
R&D Approval By:	Date: [REDACTED]				
QA Approval By:	Date: [REDACTED]				
QA Issue:	Date: [REDACTED]				
QA Audited By:	Date: [REDACTED]				
Item Code	Item No.	mg per capsule	% per Capsule (w/w)	Ingredient Name	Quantity per Batch
G134	1	37.00 ¹	21.91	White, Opaque Hard Gelatin Capsules, Size 4,	4.81 kg
PE271	2	131.87 ²	78.09	Cyclobenzaprine HCl Extended Release Beads	17.14kg
	Total	168.87			21.95 kg

¹Based on a theoretical empty capsule weight of 37.0 mg
²Equivalent to 30 mg of Cyclobenzaprine Hydrochloride (Beads based on a theoretical assay of 22.75%)

Exhibit E

Exhibit F

Cyclobenzaprine 30mg MR Capsules
Lot# PF306EA001

1 hour				8 hour				12 hour				18 hour			
CHKSTD	262100	CHKSTD	258775	CHKSTD	263356	CHKSTD	270750	CHKSTD	263356	CHKSTD	267057	CHKSTD	261737	CHKSTD	262347
1	10845	7	14041	1	205085	7	220888	1	215016	8	218838	1	232004	7	247658
2	5830	8	14418	2	215016	8	218838	2	216018	9	205793	2	245230	8	245567
3	12708	9	0	3	216018	9	205793	3	211004	10	219400	3	220533	11	211189
4	11645	10	14435	4	211004	10	219400	4	214893	12	222248	4	214893	12	222248
5	11232	11	15203	5	220533	11	211189	5	214893	12	222248	5	214893	12	222248
6	10460	12	13404	6	214893	12	222248	6	214893	12	222248	6	214893	12	222248
CHKSTD	258775	CHKSTD	262347	260581	CHKSTD	270750	CHKSTD	263356	260581	CHKSTD	267057	CHKSTD	261737	CHKSTD	262347
2 hour				12 hour				18 hour				18 hour			
CHKSTD	262347	CHKSTD	263356	CHKSTD	263356	CHKSTD	261737	CHKSTD	263356	CHKSTD	267057	CHKSTD	261737	CHKSTD	262347
1	73220	7	83060	1	232004	7	247658	1	245230	8	245567	1	26103	9	230755
2	80450	8	86176	2	245230	8	245567	2	246103	9	230755	2	26103	9	230755
3	80522	9	81274	3	246103	9	230755	3	245048	10	248980	3	251569	11	237970
4	77577	10	84346	4	245048	10	248980	4	244480	12	252556	4	251569	11	237970
5	81204	11	78231	5	244480	12	252556	5	244480	12	252556	5	251569	11	237970
6	80205	12	85540	6	251569	11	237970	6	250566	12	260602	6	251569	11	237970
CHKSTD	263356	CHKSTD	262191	262890	CHKSTD	261737	CHKSTD	261737	262890	CHKSTD	261737	CHKSTD	261737	CHKSTD	262347
4 hour				18 hour				18 hour				18 hour			
CHKSTD	262191	CHKSTD	291515	CHKSTD	261590	CHKSTD	261252	CHKSTD	261590	CHKSTD	261252	CHKSTD	261252	CHKSTD	261421
1	130693	7	156268	1	247344	7	264019	1	262134	8	262718	1	263663	9	242544
2	143494	8	158248	2	262134	8	262718	2	263663	9	242544	2	263663	9	242544
3	145159	9	151615	3	263663	9	242544	3	258431	10	265913	3	258431	10	265913
4	143021	10	150810	4	258431	10	265913	4	258448	11	254822	4	258448	11	254822
5	149222	11	149087	5	258448	11	254822	5	250566	12	260602	5	250566	12	260602
6	145149	12	160801	6	250566	12	260602	6	262476	CHKSTD	262476	CHKSTD	262476	CHKSTD	261864
8 hour				STD conc				Strength				mg/ml			
CHKSTD	268598	CHKSTD	266252	CHKSTD	267425	CHKSTD	261864	CHKSTD	268598	CHKSTD	267057	CHKSTD	268598	CHKSTD	268598
1	182178	7	197174	1	260252	8	261864	1	194500	9	196602	1	196602	9	196602
2	191272	8	194500	2	196602	9	196602	2	196727	10	196727	2	196727	10	196727
3	192435	9	186135	3	196727	10	196727	3	196802	11	196802	3	196802	11	196802
4	187095	10	197029	4	196802	11	196802	4	196823	12	196823	4	196823	12	196823
5	195802	11	186727	5	196823	12	196823	5	200502	13	200502	5	200502	13	200502
6	190602	12	196623	6	200502	13	200502	6	204502	14	204502	6	204502	14	204502
CHKSTD	266252	CHKSTD	263363	264506	CHKSTD	261864	CHKSTD	261864	264506	CHKSTD	261864	CHKSTD	261864	CHKSTD	261864
1 hour (F10)				8 hour (80-100%)				12 hour (F10)				18 hour (F10)			
1	4	7	5	1	69	7	75	1	80	7	85	1	85	7	91
2	2	8	5	2	73	8	74	2	84	9	85	2	85	9	86
3	4	9	0	3	73	9	70	3	85	9	80	3	85	9	80
4	4	10	5	4	72	10	74	4	84	10	86	4	84	10	86
5	4	11	5	5	74	11	71	5	86	11	82	5	86	11	82
6	4	12	5	6	73	12	75	6	84	12	87	6	84	12	87
Average:	4	7%		Average:	73	%	Pass	Average:	84	%	Pass	Average:	84	%	Pass
2 hour (8-40%)				12 hour (F10)				18 hour (F10)				18 hour (F10)			
1	25	7	29	1	80	7	85	1	84	9	86	1	85	9	86
2	28	8	30	2	84	9	85	2	85	9	86	2	85	9	86
3	28	9	28	3	85	9	86	3	86	10	88	3	86	10	88
4	27	10	29	4	84	10	86	4	84	10	86	4	84	10	86
5	28	11	27	5	86	11	82	5	86	11	82	5	86	11	82
6	28	12	29	6	84	12	87	6	84	12	87	6	84	12	87
Average:	28	%	Pass	Average:	84	%	Pass	Average:	84	%	Pass	Average:	84	%	Pass
4 hour (80-88%)				18 hour (80-78%)				Strength				mg/ml			
1	47	7	54	1	85	7	91	1	90	9	91	1	91	9	91
2	49	8	54	2	90	9	91	2	91	9	91	2	91	9	91
3	50	9	52	3	91	9	91	3	91	9	91	3	91	9	91
4	49	10	54	4	89	10	90	4	89	10	90	4	89	10	90
5	51	11	51	5	93	11	93	5	93	11	93	5	93	11	93
6	50	12	55	6	91	12	92	6	91	12	92	6	91	12	92
Average:	51	%	Pass	Average:	90	%	Pass	Average:	90	%	Pass	Average:	90	%	Pass
8 hour (F10)				18 hour (F10)				Strength				mg/ml			
1	61	7	67	1	85	7	91	1	90	9	91	1	91	9	91
2	65	8	66	2	90	9	91	2	91	9	91	2	91	9	91
3	65	9	63	3	91	9	91	3	91	9	91	3	91	9	91
4	63	10	67	4	89	10	90	4	89	10	90	4	89	10	90
5	67	11	64	5	93	11	93	5	93	11	93	5	93	11	93
6	64	12	68	6	91	12	92	6	91	12	92	6	91	12	92
Average:	65	%	Pass	Average:	90	%	Pass	Average:	90	%	Pass	Average:	90	%	Pass